deficiency in this amount.

PENDING CLAIMS

Following entry of this Amendment, claims 1, 9, 11-13, 15-18, and 20-26 will be pending. Claim 2 has been cancelled. New claims 21-26 have been added. Support for claims 21-26 is found as follows:

Claim	Support
21	Page 12, line 12
22	Page 21, line 9
23-26	Page 7, line 3

OBJECTION AND REJECTION UNDER 35 U.S.C. §112, FIRST PARAGRAPH

Claims 1, 2, 9, 10-13, 15-18, and 20 stand rejected, and the specification objected to, under 35 U.S.C. §112, first paragraph. The Examiner has withdrawn the rejection on the basis that the dosages used in the rat studies disclosed in the specification are different from those used in humans. The rejection on the basis that the present claims encompass autoimmune diseases beyond those for which specific clinical results have been submitted, however, is maintained. The Examiner states that there are numerous autoimmune diseases having different etiologies and symptoms and questions whether the results submitted thus far with respect to specific diseases, such as multiple sclerosis and rheumatoid arthritis, support the present claims.

An interview was held with the Examiner on January 28, 1997 regarding related applications 08/124,985, 08/480,180, and 08/463,946. During the interview, the present application was briefly discussed, at which time the Examiner mentioned that it might be helpful if applicants were to establish that a common mechanism was involved in the treatment of various autoimmune diseases according to the present invention.

Applicants have included herewith such evidence, showing that a common mechanism of action is shared in the treatment of T-cell mediated autoimmune disease according to the present invention. It is respectfully submitted that in view of this common mechanism, and applicants' pioneering work in this field, the present claims, as amended, have been shown to be enabled.

Specifically, applicants enclose the Declaration of Dr. Howard Weiner herewith establishing that the presently claimed invention involves an immunological suppression mechanism of broad applicability, namely the natural mechanism that is also involved in generating oral tolerance to the diverse antigens present in food. The invention is independent of the particular autoantigen in the way that oral tolerance in nutrition (i.e., tolerance to food antigens) is independent of the particular antigens. The immune response in T-cell mediated autoimmune diseases is suppressed generally as the response to food antigens is generally suppressed. Dr. Weiner explains the common mechanism involved in detail.

Dr. Weiner also explains that the mechanism involved in the invention for treating autoimmune disease has been determined to have even broader applicability than that claimed.

The autoantigens used to treat T-cell mediated or T-cell dependent autoimmune disease are a subset of a larger group of antigens termed "bystander antigens" that have been found to treat these diseases. For this additional reason, the applicability of the present invention to the diseases encompassed has been established.

The Examiner is referred to Dr. Weiner's declaration for additional discussion of the outstanding enablement rejection.

It is respectfully submitted that applicants have met all applicable requirements with respect to demonstrating that their invention in fact functions to treat T cell-mediated or T cell-dependent autoimmune disease, as presently claimed.

Withdrawal of the objection to the specification and rejection of remaining claims 1, 9, 10-13, 15-18, and 20 under 35 U.S.C. §112, first paragraph is respectfully requested.

REJECTION UNDER 35 U.S.C. §103

a. Claims 1, 2, 9, 11-13, 15-18 and new claims 21-24 and 26

Claims 1, 2, 9, 11-13, 15-18 and 20 stand rejected under 35 U.S.C. §103 as obvious over Campbell et al. in view of Whitacre et al., and/or Nagler-Anderson et al. The Examiner states that the arguments advanced in the prior response are convincing with respect to this rejection. The rejection is maintained, however, solely because of the rejection of these claims on the basis that there is no support for the limitation that was added in the previous response concerning elicitation of T-cells. The new rejection is addressed below. Assuming that

the new rejection is withdrawn, the rejection under 35 U.S.C. §103 should be withdrawn as well.

b. Amended claim 20 and new claim 25

Amended claim 20 and dependent claim 25 do not contain the limitation objected to by the Examiner under §112, i.e., "said suppression comprising elicitation of suppressor T cells specific to said administered antigen." These claims are clearly patentable under §112. Furthermore, it is submitted that the deleted limitation is not required to establish patentability over the cited references, particularly in view of the amendment herein to recite treatment of an individual suffering from T-cell mediated or T-cell dependent autoimmune disease.

The combination of Campbell and Whitacre and/or Nagler-Anderson does not provide any reasonable expectation of success that the method of these claims would be successful, and therefore these claims are non-obvious. (These reasons are also applicable to claims 1, 2, 9, 11-13, 15-18, 21-24 and 26, but those claims are already indicated to be patentable over the cited references once support is found under §112 for the "suppressor" language.)

As believed has been previously established, Whitacre and Nagler-Anderson are the only relevant references for the oral or enteral administration of the claims. However, neither reference provides any basis for predicting that treatment with an autoantigen after the relevant disease has been induced (in the relevant animal model) would be successful. In fact, as discussed further below, these references tend to teach away from this result (which was

successfully achieved by the present inventors).

Whitacre et al. provide no basis for predicting that treatment with MBP after EAE has been induced would be successful. Whitacre et al. only disclose results for rats that were orally administered MBP, and then challenged with MBP-CFA, i.e., the disease was induced after oral administration. No experiments are described wherein EAE was treated by oral MBP, i.e., where oral MBP was administered after immunization with the disease-inducing MBP-CFA preparation.

Furthermore, examination of the Bitar thesis (reference 19 submitted with applicants' IDS filed 12/17/96) shows that Whitacre et al. were, in fact, unsuccessful in treating the disease when it was induced. Specifically, Bitar (who is the other named author of the Whitacre reference) describe experiments in which MBP was orally administered at the same time that the disease was induced. These experiments were unsuccessful in suppressing clinical disease activity (page 67, line 7). The Bitar thesis does not describe any attempts to administer oral MBP after the disease was induced. It appears that Bitar was discouraged from performing these experiments because of the unsuccessful results obtained when oral MBP was administered at the same time the disease was induced.

Applicants, on the other hand, were successful in treating the disease after it was induced. See the results, e.g., at page 18, in which oral administration of MBP after immunization was shown to suppress the clinical disease.

Bitar, in fact, specifically stated that experiments showing effective treatment of

disease after it was induced (which she did not do) would be important in determining the applicability of oral administration of MBP to treatment of MS:

> Other questions are: . . . to investigate the effectiveness of orally induced tolerance to MBP in suppressing ongoing EAE . . . [These] experiments would be important in considering oral MBP for therapeutic trials in MS. (p. 88)

It appears clear from these statements that the Whitacre reference, properly read as a whole, could not have allowed one to predict that the present invention would work with any reasonable expectation of success.

Similarly, Nagler-Anderson et al. specifically reported failure to treat mice in which autoimmune disease was already induced:

In the present studies (data not shown) eight intragastric administrations of type II collagen were given between days 10 and 29 after immunization with type II collagen in complete Freund's adjuvant [i.e., after the disease was induced] did not result in decreased incidence or severity of CIA.

Thus, as with the Whitacre reference, Nagler-Anderson et al. failed to achieve the successful results obtained by the inventors in treating disease after it had been induced, and tend, if anything, to teach away from the presently claimed invention.

For these reasons, applicants respectfully submit that new claims 20 and 25, which recite treatment of an individual suffering from T-cell mediated autoimmune disease, are also patentable over the cited art.

REJECTION UNDER 35 U.S.C. §112, FIRST PARAGRAPH

Claims 1, 2, 9, 11-13, 15-18 and 20 stand rejected on the basis that there is no support in the present specification for the limitation in independent claims 1 and 20 concerning elicitation of suppressor T-cells. As noted above, this language has been removed from claim 20 on the basis that it is not necessary for patentability. Applicants respectfully traverse this rejection with respect to the remaining rejected claims.

The specification states, at page 8, line 4, that "The cells responsible for both the suppression of the diseases and suppression of antigen-specific cellular responses in vitro are of T-cell origin and are **suppressor**-cytotoxic CD8+**T lymphocytes**." (emphasis added)

In addition, the specification at Example 15 shows the "Determination of the Cell Type Responsible for the Suppression of IgG Production In Vitro". It was concluded that "CD8+ cells were responsible for suppression" on the basis of "adoptive transfer" and other experiments. In other words, the suppression comprises elicitation of suppressor T-cells.

Elicitation of suppressor T-cells is also disclosed at page 7, line 15.

In addition, the method of the invention practiced in the Examples inherently involves elicitation of suppressor T-cells (as demonstrated in Example 15), and support could be found on this basis alone. (*Kennecott Corp. v. Kyocera International Inc.*, 5 USPQ2d 1194 (Fed. Cir. 1987)).

For these reasons, withdrawal of the rejection of claims 1, 2, 9, 11-13, 15-18, and 20 on the basis that there is no support in the specification for "said suppression comprising

elicitation of suppressor T cells specific to said administered antigen" is respectfully requested.

INFORMATION DISCLOSURE STATEMENT

In reviewing the present file, applicants note that the Form 1449 submitted with the Information Disclosure Statement of October 24, 1996 has not been returned to applicants. Applicants request that the Examiner return the initialed copy of the form 1449 (i.e., and consider any references that have not been considered).

CONCLUSION

This application is respectfully submitted to now be in condition for allowance. Issuance of a notice to that effect is respectfully requested.

Respectfully submitted,

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